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Efficacy and safety of corticosteroids for stroke and traumatic brain injury: a systematic review and meta-analysis

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Abstract

Background Corticosteroids are frequently used in practice to treat patients with neurological disorders. However, its effect for stroke and traumatic brain injury (TBI) remains controversial. This study aimed to systematically review and evaluate efficacy and safety of corticosteroids for the treatment of stroke and TBI.

Methods We searched Ovid-Medline and Ovid-Embase databases for randomised controlled trials (RCTs) and cohort studies evaluating the efficacy and safety of corticosteroids in patients with ischaemic stroke, intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH) or TBI. The treatment intervention was corticosteroid, and the control was placebo or routine care. Outcome measures were death, functional outcomes and adverse events. We calculated odds ratio (OR) and 95% confidence interval (CI) for the effect size, pooled the results using random-effects modelling, and assessed heterogeneity by I^2 statistic.

Results We identified 47 studies (41 RCTs and 6 cohort studies). Nine studies enrolled patients with ischaemic stroke ($n=2806$), 6 studies for ICH ($n=1229$), 1 study recruited both ischaemic stroke ($n=13$) and ICH ($n=27$), 10 studies for SAH ($n=1318$) and 21 studies for TBI ($n=12,414$). Dexamethasone was the most used corticosteroid (28 studies). Corticosteroids reduced risk of death at 3 months after ischaemic stroke ($n=1791$; 31% vs. 26%, OR 0.77, 95% CI 0.62–0.95; $df=1$, $I^2=0\%$) and after ICH (1 study; $n=850$; 44% vs. 27%, OR 0.48, 95% CI 0.35–0.64), had no effect on death at 1 month after SAH (1 study; $n=140$; 22% vs. 32%, OR 1.73, 95% CI 0.81–3.68), and increased risk of death at 6 months after TBI ($n=10,755$; 23% vs. 27%, OR 1.20, 95% CI 1.10–1.32; $df=6$, $I^2=0\%$). The pooled analyses found no significant effect of corticosteroids on functional outcome after ischaemic stroke, ICH, SAH or TBI, respectively.

Conclusion Corticosteroids reduced the risk of death and in selected patients with stroke, such as those with large artery occlusion after thrombectomy, but increased the risk of death after TBI, had no effect on functional outcomes. Further trials are needed to identify individual stroke patients who may benefit from corticosteroids.

Systematic review registration International Prospective Register of Systematic Reviews (CRD42023474473).

Keywords Corticosteroids, Stroke, Traumatic brain injury, Meta-analysis

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Introduction

Vascular and traumatic brain injury (TBI) are leading causes of death and disability worldwide [1, 2]. Despite distinct aetiologies of ischaemic stroke, intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH), and TBI, these conditions share common pathophysiological mechanisms for secondary injuries, such as neuroinflammation and disruption of blood–brain barrier [3, 4]. Corticosteroids are frequently used in practice for patients with neurological disorders [5]. Given the anti-inflammatory and anti-oedematous properties [6], corticosteroids are recommended for reducing mortality in tuberculosis meningitis [7]. However, their efficacy in improving outcomes for stroke and TBI remains uncertain.

Previous systematic reviews and meta-analyses have reported insufficient evidence for the benefit or adverse effect of corticosteroids in patients with ischaemic stroke [8], ICH [9, 10], or SAH [9, 11]. Studies included in these previous reviews have limitations of generally small sample size, and that some studies were conducted before the application of brain CT. Thus, there was uncertainty in the diagnosis of stroke and in differential diagnosis of ischaemic and haemorrhagic stroke. Similarly, the effect of corticosteroids for TBI was inconclusive until the publication of CRASH (corticosteroid randomisation after significant head injury) trial [12], which unexpectedly showed that corticosteroids increased mortality after TBI [13, 14]. Furthermore, a recent trial investigated corticosteroids as adjunct to endovascular thrombectomy for large-vessel occlusion stroke was recently published [15]. As a result, evidence from previous reviews remains inconclusive and may not be applicable to the contemporary clinical practice, such as the treatment for ischaemic stroke in an era of reperfusion. In addition, the emerging large scale trials may provide more robust evidence. Moreover, we hypothesised that different pathological types of strokes might have different response to corticosteroids, which has not been investigated previously.

Therefore, we conducted a comprehensive systematic review and meta-analysis to assess efficacy and safety of corticosteroids for the treatment of ischaemic stroke, ICH, SAH and TBI, with an aim to provide more reliable evidence for contemporary practice.

Methods

This systematic review was registered in PROSPERO (https://www.crd.york.ac.uk/prospero/; Unique identifier: CRD42023474473) and is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [16].

Literature search

We searched Ovid-Medline and Ovid-Embase databases from inception to September 19, 2023, without language restrictions, using key words ((corticosteroids) AND (ischaemic stroke OR intracerebral haemorrhage OR subarachnoid haemorrhage OR traumatic brain injury)). We also screened reference lists of included studies and relevant reviews and contacted experts in the field for any further articles (full search strategies in Table S1). We did not include grey literature.

Eligibility criteria

We included randomised controlled trials (RCTs) and cohort studies (a) of patients with ischaemic stroke, ICH, SAH, or TBI; (b) investigated efficacy and/or safety of corticosteroids (any type of medication, any route of administration, and any dose, frequency and duration of treatment); (c) comparison interventions were placebo or standard medical treatment; (d) reported outcomes of death, functional outcomes, or adverse events at any time after treatment; and (e) published as full texts in English language. We excluded studies comparing corticosteroids with other anti-inflammatory or anti-oedematous agents. For studies with overlapping populations, we had planned to extract data from the study with the largest sample size; for studies with the same sample size, we had planned to extract data from the latest published study, although none of the included studies met this situation.

Study selection, bias assessment and data extraction

Two researchers (LH, JL) independently screened title and abstract of citations retrieved from electronic search. Full texts were obtained for potentially eligible studies. If there were two or more publications derived from one study, we included the publication with most complete data or pooled data from all publications. Any discrepancies in study selection were resolved through discussion or consulting a third researcher (YW or SW). Two reviewers (LH, JL) independently assessed risk of bias according to Cochrane Handbook for Systematic Reviews of Interventions for RCTs [17] and The Newcastle–Ottawa Scale (NOS) for cohort studies [18]. We extracted data of article information, study design, sample size, baseline characteristics, treatment and control interventions, outcome measures and results.

Outcome measures

The primary outcome was death at 3 months. If data for 3 months were not available, we used data of death in the order of at 6 months, 1 year or other assessment time as reported. Secondary outcomes were functional outcomes, neurological deterioration, requirement for

neurosurgical intervention, and neurological complications (e.g. brain swelling and haemorrhagic transformation), adverse drug events (e.g. infection, gastrointestinal bleeding, electrolytes disturbance, et al.) and biochemical markers in blood serum or cerebrospinal fluid.

Statistical analysis

We performed statistical analysis separately for patients with ischaemic stroke, ICH, SAH and those with TBI. For dichotomous outcome measures, we calculated odds ratio (OR) with 95% confidence interval (CI). For continuous outcome measures, we calculated mean difference (MD) and 95% CI. We estimated pooled effect size by random-effects modelling and assessed the degree of heterogeneity by I^2 statistic (with 25% for low, 50% for moderate and 75% for high heterogeneity). We conducted sensitivity analyses for RCTs, by calculating risk ratio (RR) or MD for the effect size. Publication bias was examined by funnel plots and Egger's test for any outcome measure if reported in more than 10 studies [19]. We performed subgroup analyses for the primary outcome to assess the effect of treatment dose and duration ($\leq$7 days vs. >7 days). The treatment dose of different corticosteroids was calculated to an equivalent dose of dexamethasone for an adult patient with 70 kg body weight; all included studies were dichotomised as low dose or high dose by the median dose used in all studies as the cut-off value. We had intended to conduct a network meta-analysis to compare between different corticosteroids; however, this was not performed due to the limited number of included studies. Data were analysed using Review Manager 5.3 (Cochrane Collaboration), Stata 18.0 (Stata Corp, College Station, Texas, USA), and R version 4.3.3.

Results

Study characteristics

We obtained 7919 citations from electronic search, removed 954 duplicated citations and performed title and abstract screening for 6965 citations, obtained full texts for 64 studies, and finally included 47 studies (41 RCTs and 6 cohort studies; Fig. 1) [13–15, 20–63]. Of 47 studies, 13 studies were published in 1970s, 16 studies in 1980s, 5 studies in 1990s and 13 studies after 2000. Nineteen studies were from Europe, 16 studies from North America, 9 studies from Asia, 1 study from Africa, 1 study from Oceania and 1 study from South America (Table 1).

Nine studies enrolled patients with ischaemic stroke (n=2806; mean or median age 66–76 years; male 44.4–56.7%) and 6 studies for ICH (n=1229; mean or median age 58–73 years; male 51.6–62.5%) and 1 study recruited

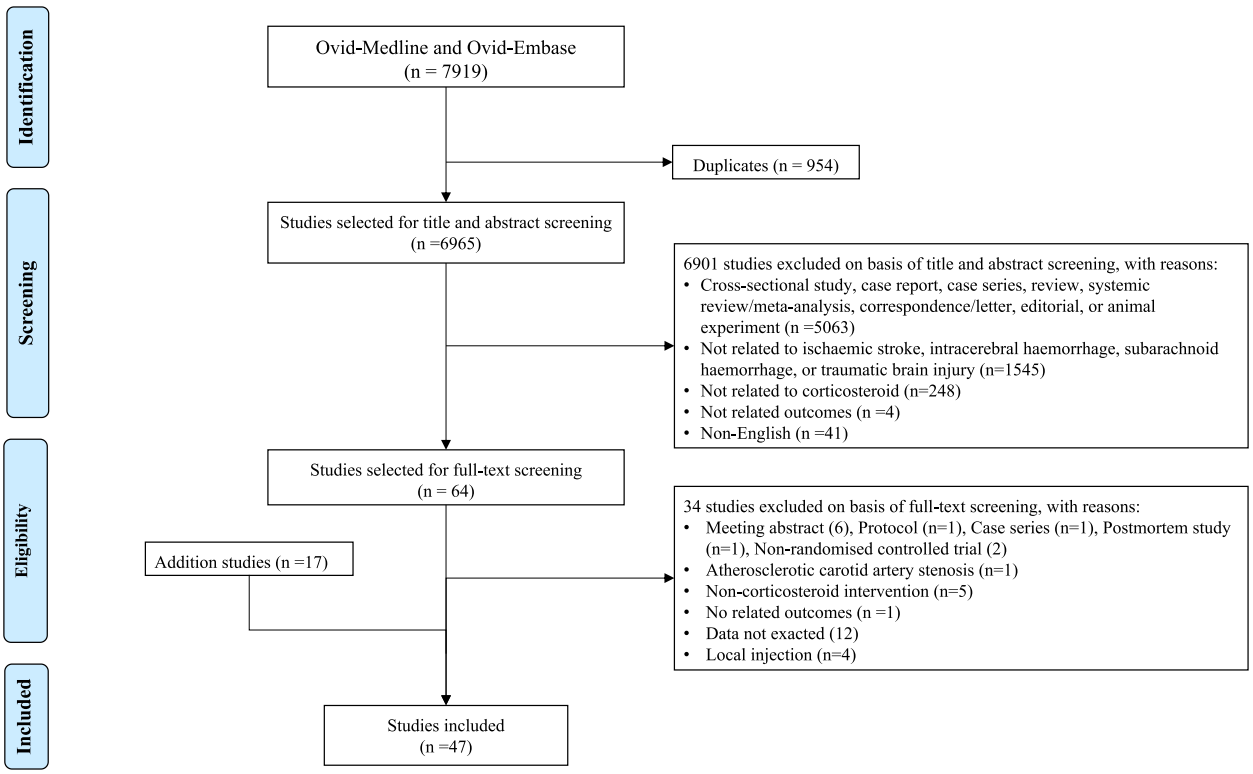
Identification
Screening
Eligibility
Included
Ovid-Medline and Ovid-Embase
(n = 7919)
Duplicates (n = 954)
Studies selected for title and abstract screening
(n =6965)
6901 studies excluded on basis of title and abstract screening, with reasons:
• Cross-sectional study, case report, case series, review, systemic review/meta-analysis, correspondence/letter, editorial, or animal experiment (n =5063)
• Not related to ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, or traumatic brain injury (n=1545)
• Not related to corticosteroid (n=248)
• Not related outcomes (n =4)
• Non-English (n =41)
Studies selected for full-text screening
(n = 64)
34 studies excluded on basis of full-text screening, with reasons:
• Meeting abstract (6), Protocol (n=1), Case series (n=1), Postmortem study (n=1), Non-randomised controlled trial (2)
• Atherosclerotic carotid artery stenosis (n=1)
• Non-corticosteroid intervention (n=5)
• No related outcomes (n =1)
• Data not exacted (12)
• Local injection (n=4)
Addition studies (n =17)
Studies included
(n =47)

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the study

Table 1 Characteristics of randomised controlled trials and cohort studies of the effect of corticosteroids on treatment of stroke and traumatic brain injury

Type of participant	Study ID	Design	Sample size	Treatment vs. control	Outcome
IS	Yang 2024 China	RCT	1680	MP vs. Placebo	Death Functional outcome Neurological complications Hyperglycaemia/Diabetes mellitus Infections Gastrointestinal bleeding
	Norris 1986 Canada	RCT	113	DXM vs. Placebo	Death
	Gupta 1978 India	RCT	30	Beta vs. Placebo	Death
	McQueen 1978 New Zealand	RCT	48	Beta vs. Placebo	Death
	Mulley 1978 UK	RCT	118	DXM vs. Placebo	Death Functional outcome
	Santambrogio 1978 Italy	RCT	166	DXM vs. Standard medical treatment	Neurological deficit improvement
	Norris 1976 Canada	RCT	41	DXM vs. Placebo	Death Gastrointestinal bleeding
	Bauer 1973 USA	RCT	54	DXM vs. Placebo	Death Gastrointestinal bleeding
	Reuck 1988 Switzerland	Cohort	556	Steroids vs. Placebo	Death Cardiac problems Stroke progression Gastrointestinal bleeding Infections Hyperglycaemia/Diabetes mellitus
ICH	Sm 2008 Iran	RCT	200	DXM vs. Placebo	Death Electrolytes disturbance Infections Hyperglycaemia/Diabetes mellitus Gastrointestinal bleeding Rising of blood pressure
	Desai 1998 India	RCT	26	DXM vs. Placebo	Death Functional outcome Gastrointestinal bleeding Infections Hyperglycaemia/Diabetes mellitus
	Poungvarin 1987 Thailand	RCT	93	DXM vs. Placebo	Death Functional outcome Requirement for neurosurgical intervention Gastrointestinal bleeding Infections Hyperglycemia/Diabetes mellitus
	Tellez 1973 USA	RCT	40	DXM vs. Placebo	Death Gastrointestinal bleeding
	Hooshmand 1972 USA	RCT	20	DXM vs. Placebo	Death
	Zaganas 2011 Greece	Cohort	850	DXM vs. Placebo	Death
IS/ICH	Ogun 2001 Nigeria	RCT	40	DXM vs. Placebo	Death Functional outcome Infections
SAH	Gomis 2010 France	RCT	95	MP vs. Placebo	Functional outcome Cerebral vasospasm
	Katayama 2007 Japan	RCT	71	HC vs. Placebo	Functional outcome Cerebral vasospasm Gastrointestinal haemorrhage
	Moro 2003 Japan	RCT	28	HC vs. Placebo	Functional outcome Electrolytes disturbance Cerebral vasospasm Hyperglycaemia/Diabetes mellitus Gastrointestinal haemorrhage

Table 1 (continued)

Type of participant	Study ID	Design	Sample size	Treatment vs. control	Outcome
	Mori 1999 Japan	RCT	30	Fludrocortisone vs. Placebo	Functional outcome Cerebral vasospasm Electrolytes disturbance Gastrointestinal haemorrhage Hyperglycaemia/Diabetes mellitus Glucose
	Hasan 1989 Netherlands	RCT	91	Fludrocortisone vs. Placebo	Cerebral vasospasm Electrolytes disturbance
	Hashi 1988 Japan	RCT	140	HC vs. Placebo	Death Functional outcome Hyperglycaemia/Diabetes mellitus Gastrointestinal bleeding
	Miller 2021 USA	Cohort	206	DXM vs. No corticosteroids	Functional outcome Cerebral vasospasm Infections Hyperglycaemia/Diabetes mellitus Requirement for neurosurgical intervention Neurological complications
	Mohney 2018 USA	Cohort	309	DXM vs. No corticosteroids	Poor functional outcome Cerebral vasospasm Infections
	Czorlich 2017 Germany	Cohort	306	DXM vs. No corticosteroids	Death Functional outcome Hyperglycaemia/Diabetes mellitus Infections
	Chyatte 1987 USA	Cohort	42	MP vs. No MP	Death Functional outcome Cerebral vasospasm Gastrointestinal haemorrhage Hyperglycaemia/Diabetes mellitus
TBI	Asehnoune 2014 France	RCT	328	Corticosteroids vs. Placebo	Death Infections Requirement for neurosurgical intervention
	Roquilly 2011 France	RCT	149	HC vs. Placebo	Infections
	Edwards 2005 UK	RCT	9673	MP vs. Placebo	Death Functional outcome
	Grumme 1995 Germany	RCT	396	Triamcinolone vs. Placebo	Death Functional outcome Gastrointestinal bleeding Infections Hyperglycaemia/Diabetes mellitus
	Zarate 1995 Spain	RCT	60	Corticosteroids vs. Symptomatic treatment	Death
	Gaab 1994 Germany	RCT	298	DXM vs. Placebo	Death Functional outcome Gastrointestinal bleeding Infections
	Stubbs 1989 USA	RCT	152	MP vs. Placebo	Death Gastrointestinal bleeding
	Kloti 1987 Switzerland	RCT	24	DXM vs. No corticosteroids	Death Functional outcome
	Chacon 1987 Venezuela	RCT	10	DXM vs. Placebo	Death
	Zagara 1987 Italy	RCT	24	DXM vs. No corticosteroids	Death
	Braun 1986 USA	RCT	66	DXM vs. Placebo	Infections

Table 1 (continued)

Type of participant	Study ID	Design	Sample size	Treatment vs. control	Outcome
	Dearden 1986 UK	RCT	130	DXM vs. Placebo	Death Functional outcome Gastrointestinal bleeding Blood glucose
	Giannotta 1984 USA	RCT	88	MP vs. No MP	Death Functional outcome
	Braakman 1983 Netherlands	RCT	161	DXM vs. Placebo	Death Functional outcome Gastrointestinal bleeding Infections
	Saul 1981 USA	RCT	100	MP or DXM vs. no drug	Death Functional outcome
	Pitts 1980 USA	RCT	275	DXM vs. Placebo	Death Functional outcome
	Cooper 1979 USA	RCT	76	DXM vs. Placebo	Functional outcome Neurological complications Gastrointestinal bleeding Infections Hyperglycaemia/Diabetes mellitus
	Hernesniemi 1979 Finland	RCT	164	Beta vs. Placebo	Death Functional outcome Hyperglycaemia/Diabetes mellitus Gastrointestinal bleeding
	Faupel 1977 Germany	RCT	95	DXM vs. Placebo	Death Functional outcome Gastrointestinal bleeding
	Alexander 1972 USA	RCT	110	DXM vs. Placebo	Death Gastrointestinal bleeding
	Ransohoff 1972 USA	RCT	35	MP vs. Placebo	Death

Beta Betamethasone *DXM* Dexamethasone, *HC* Hydrocortisone, *IS* Ischaemic stroke, *ICH* Intracerebral haemorrhage, *MP* Methylprednisolone, *RCT* Randomised controlled trials, *SAH* Subarachnoid haemorrhage, *TBI* Traumatic brain injury

both ischaemic stroke ($n=13$) and ICH ($n=27$), 10 studies for SAH ($n=1318$; mean or median age 50–59 years; male 29.5–56.7%) and 21 studies for TBI ($n=12{,}414$; mean or median age 7–36 years; male 71.5–83.2%). For patients with ischaemic stroke (10 studies), the most commonly used corticosteroid was dexamethasone (7 studies), followed by methylprednisolone (2 studies) and betamethasone (2 studies). All 7 studies of ICH used dexamethasone. For patients with SAH (10 studies), 3 studies used dexamethasone, 3 studies used hydrocortisone, 2 studies used methylprednisolone, and 2 studies used fludrocortisone. For patients with TBI (21 studies), dexamethasone was used in 11 studies, followed by methylprednisolone (5 studies), hydrocortisone (2 studies), betamethasone (1 study), triamcinolone (1 study) and unspecified type of corticosteroids (1 study; Table S2). The median value of the total dose of corticosteroids used in the included studies was 200 mg dexamethasone (standardised dose) for an adult with 70 kg body weight.

We found 6 ongoing RCTs and 4 observational studies of corticosteroids for stroke or TBI, which focused on patients with stroke combined with inflammatory conditions, for perioperative patients, targeting neurological complications, or exploring inflammatory biomarkers (Table S3).

Risk of bias and publication bias

Of 41 published RCTs, 9 (22%) trials were at low risk of bias, 2 (5%) trials had a high risk of bias and other 30 studies had uncertain risk of bias, with risks mainly in random sequence generation and allocation concealment (Figure S1). Six cohort studies all achieved a score of 8 or 9 on NOS, indicating good methodological quality (Table S4). We detected publication bias for the report of death after TBI, where studies with small sample size tend to report more favourable outcomes (18 studies, $n=22{,}594$, $p=0.041$; Figure S2A). There was no publication bias for functional outcome in patients with TBI (12 studies, $n=11{,}707$, $p=0.210$; Figure S2B), infections (10 studies, $n=2194$, $p=0.523$; Figure S2C), gastrointestinal bleeding (22 studies, $n=4638$, $p=0.408$; Figure S2D) or hyperglycaemia/diabetes mellitus (14 studies, $n=3851$, $p=0.237$; Figure S2E).

Death

For patients with ischaemic stroke, corticosteroids reduced the risk of 3-month death (2 studies; $n=1791$; 31% vs. 26%, OR 0.77, 95% CI 0.62–0.95; $df=1$, $I^2=0\%$), and showed no effect on death in hospital, at 1 month, or at 1 year (Fig. 2A). For patients with ICH, corticosteroids reduced risk of 3-month death (1 study; $n=850$; 44% vs. 27%, OR 0.48, 95% CI 0.35–0.64), and showed no effect on death in hospital, at 1 month, or at 6 months (Fig. 2B). For patients with SAH, there was no difference between corticosteroids and control groups on death at 1 month (1 study; $n=140$; 22% vs. 32%, OR 1.73, 95% CI 0.81–3.68) (Fig. 2C). For patients with TBI, corticosteroids increased the risk of death at 6 months (7 studies; $n=10{,}755$; 23% vs. 27%, OR 1.20, 95% CI 1.10–1.32; $df=6$, $I^2=0\%$) and at 1 month (2 studies; $n=10{,}125$, 18% vs. 22%, OR 1.22, 95% CI 1.11–1.35; $df=1$, $I^2=0\%$), and showed no effect on death at other time points (Fig. 2D).

For the effect of corticosteroids on 3-month death after ischaemic stroke, there was no significant between-group heterogeneity between subgroups of patients with different doses (≤200 mg vs. >200 mg dexamethasone, $df=1$, p for heterogeneity = 0.68) or between subgroups of patients with different treatment duration (≤7 days vs. >7 days, $df=1$, p for heterogeneity = 0.68). For the effect of corticosteroids on 6-month death after TBI, there was no significant between-group heterogeneity between dose subgroups (≤200 mg vs. >200 mg dexamethasone, $df=1$, p for heterogeneity = 0.66) or between subgroups with different treatment duration (≤7 days vs. >7 days, $df=1$, p for heterogeneity = 0.69) (Table S5).

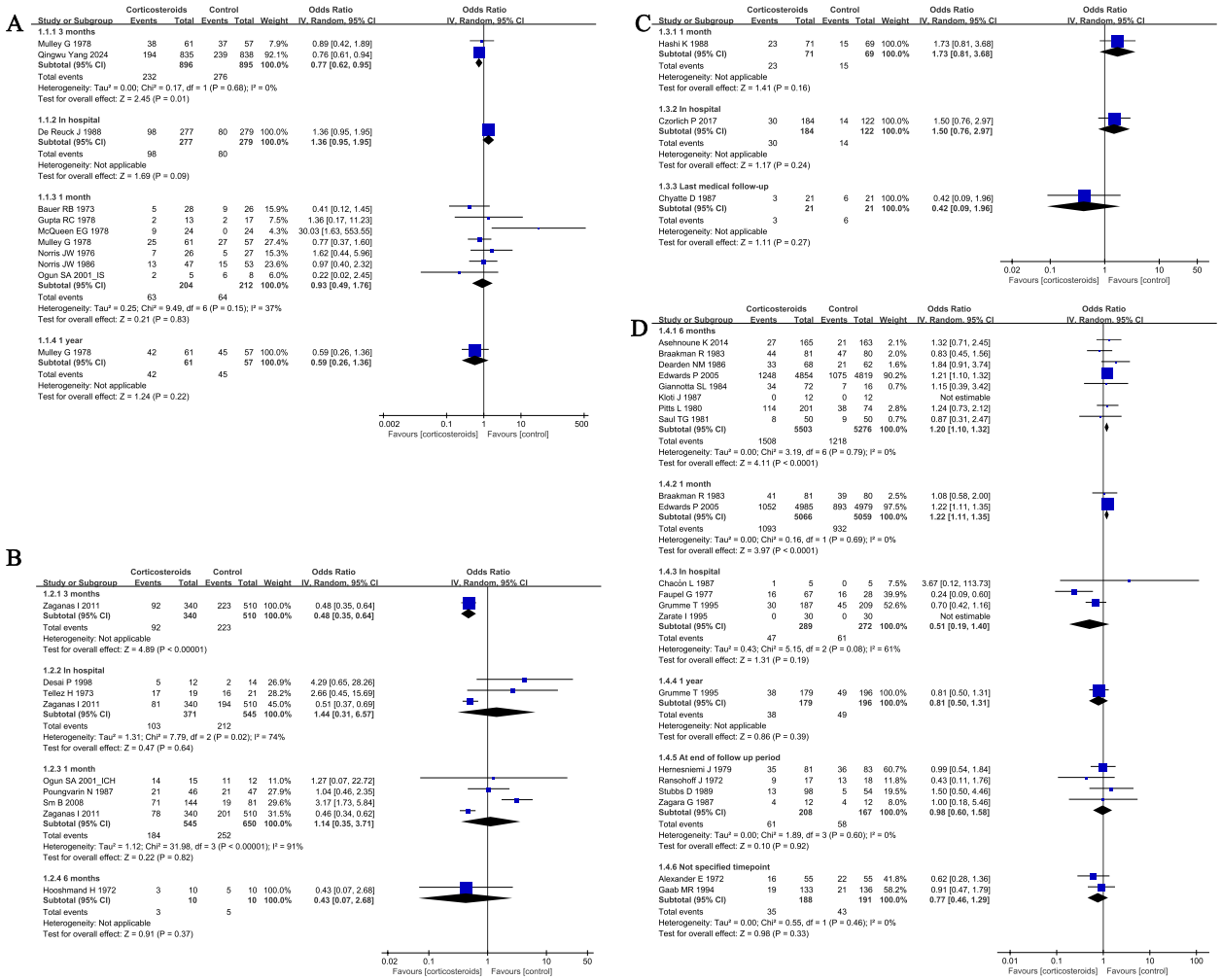

Fig. 2 Forest plots for the effect of corticosteroids on death between the corticosteroid group and the control group in patients with stroke or traumatic brain injury. A Ischaemic stroke, B intracerebral haemorrhage, C subarachnoid haemorrhage, or D traumatic brain injury. Pooled odds ratio and 95% confidence intervals (CI) were calculated using random-effects modelling

Functional outcome

Compared to control group, corticosteroids did not have significant effect on functional outcomes in ischaemic stroke (Fig. 3A), ICH (Fig. 3B), SAH (Fig. 3C) or those with TBI (Fig. 3D).

Neurological complications

Individual studies explored the effect of corticosteroids on neurological complications. Corticosteroids reduced risk of symptomatic intracranial haemorrhage after ischaemic stroke (1 study; $n=1653$, OR 0.71, 95% CI 0.52–0.99) but had no effect on radiological intracranial haemorrhage (1 study; $n = 1653$; OR 1.05, 95% CI 0.86–1.28). In patients with TBI, corticosteroids had no effect on intracranial pressure (1 study; $n=51$; OR 0.37, 95% CI 0.11–1.28). In patients with SAH, there was no difference between corticosteroids and control groups in delirium (1 study; $n=206$; OR 0.69, 95% CI 0.26–1.87), hypodensities on computed tomography (1 study; $n=95$; OR 1.13, 95% CI 0.46–2.80), delayed cerebral ischaemia (3 studies; $n=606$; OR 0.88, 95% CI 0.60–1.30; $df=2$, $I^2=0\%$), or symptomatic cerebral vasospasm (5 studies; $n=266$; OR 0.63, 95% CI 0.34–1.16; $df=4$, $I^2=0\%$).

Other clinical outcomes

Corticosteroids increased risks of stroke progression (1 study; $n=556$; OR 2.40, 95% CI 1.54–3.75) and had no effect on the improvement of neurological deficit (1 study; $n=89$; OR 0.84, 95% CI 0.36–1.95) after ischaemic stroke. There was no difference between corticosteroids and control groups in requirement of decompressive craniectomy after ICH (1 study; $n=93$; OR 1.02, 95% CI 0.06–16.85) or TBI (1 study; $n=328$; OR 0.99, 95% CI 0.51–1.91), or external ventricular drain (1 study; $n=206$; OR 0.51, 95% CI 0.23–1.12) or placement of a ventriculoperitoneal shunt (1 study; $n=206$; OR 0.79, 95% CI 0.21–2.98) after SAH.

Adverse drug events

Fourteen out of 47 studies systematically investigated adverse drug events. For patients with ischaemic stroke, corticosteroids reduced risk of pneumonia (1 study; $n=1680$; OR 0.70, 95% CI 0.58–0.85), and increased risk of hyperglycaemia (2 studies; $n=2236$; OR 1.55, 95% CI 1.02–2.34; $df=1$; $I^2=0\%$). For patients with ICH, corticosteroids increased risks of fever (1 study; $n=225$; OR 2.06, 95% CI 1.12–3.77), reduced risks of hyperkalaemia (1 study; $n=225$, OR 0.16, 95% CI 0.05–0.53), increased daily potassium excretion (1 study, $n=28$; MD

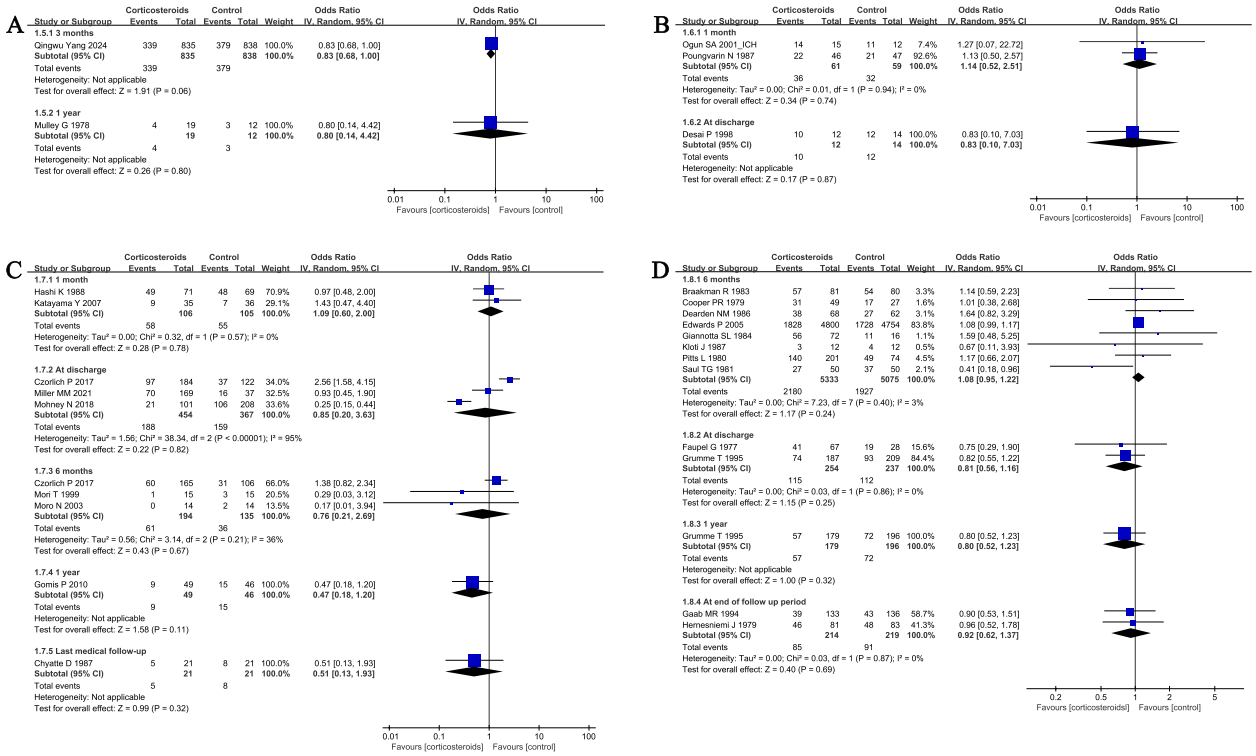

Fig. 3 Forest plots for the effect of corticosteroids on functional outcome between the corticosteroid group and the control group in patients with stroke or traumatic brain injury. A Ischaemic stroke, B intracerebral haemorrhage, C subarachnoid haemorrhage, or D traumatic brain injury. Pooled odds ratio and 95% confidence intervals (CI) were calculated using random-effects modelling

54.10 mEq/day, 95% CI 43.68–64.52), reduced serum level of potassium (1 study; $n=28$; MD −0.40 mEq/day, 95% CI −0.47 to 0.33), and reduced serum total protein (1 study; $n=28$; MD −0.40 mg/dL, 95% CI −0.47 to 0.33) (Table 2).

For patients with SAH, corticosteroids reduced the risk of negative cumulative sodium balance in first 6 days of treatment (1 study; $n=77$; OR 0.37, 95% CI 0.15–0.92) and in the entire 12-day of treatment period (1 study; $n=61$; OR 0.17, 95% CI 0.06–0.53), reduced the risk of hyponatremia (2 studies; $n=58$; OR 0.09, 95% CI 0.02–0.58; $df=1$, $I^2=0\%$) and polyuria (1 study; $n=28$; OR 0.05, 95% CI 0.00–0.90), and increased the risk of hypokalaemia (2 studies; $n=58$; OR 4.62, 95% CI 1.45–14.70; $df=1$, $I^2=0\%$). For patients with TBI, one study found corticosteroids increased levels of blood glucose (1 study; $n=104$; MD 1.49 mmol/L, 95% CI 1.38–1.60) (Table 2).

Sensitivity analyses

Sensitivity analyses of RCTs showed consistent results in the effect of corticosteroids on reducing death after ischaemic stroke and increasing death after TBI, but no significant effect on death after ICH or SAH (Table S6).

Discussion

This systematic review and meta-analysis included 47 studies, where one-fourth of studies were conducted after 2000 and one-third of studies systematically investigated adverse drug events. Dexamethasone was the most commonly used corticosteroid for stroke and TBI. Despite limited data and generally small sample sizes of the included studies, corticosteroids reduced risk of death after ischaemic stroke but increased risk of death after TBI and showed no effect on death after haemorrhagic stroke. There was no effect on functional outcome in these conditions. Corticosteroids increased the risk of fever, hyperglycaemia and disturbance in electrolyte metabolism.

A Cochrane review published in 2011 evaluated the efficacy of corticosteroids in patients with suspected ischaemic stroke [8], concluding that there was insufficient evidence to support an effect on death or functional outcomes, and there were limited studies reporting adverse events. The current review additionally included recently published large trials [15]. This trial potentially drove the pooled benefit on mortality. However, it found no effect of corticosteroids on 3-month functional outcomes. Furthermore, this trial tested corticosteroids as adjunct to thrombectomy for stroke patients, which was distinct from previous trials in both the studied population and intervention. Despite this, the study indicated the potential of corticosteroids to benefit some patients with ischaemic stroke, and future studies are needed to explore the characteristics of individuals who might benefit from corticosteroid treatment. For example, a trial is ongoing to investigate methylprednisolone adjunctive to endovascular treatment for large infarct cores (NCT06360458).

The current review indicated that corticosteroids decreased the risk of death after ischaemic stroke but increased the risk of death after TBI and had no effect on death after ICH or SAH. These observations may be linked to the anti-inflammatory mechanisms of corticosteroids [6]. Brain swelling is a leading cause of death during the acute phase of both ischaemic stroke and ICH [3, 64]. In ischaemic stroke, brain oedema is evolving from cytotoxic oedema to vasogenic oedema, where the latter was associated with disruption of blood–brain barrier. Corticosteroids are effective in reducing vasogenic cerebral oedema by mitigating the damage of blood–brain barrier [65]. For patients with ICH, brain swelling is caused by expansion of haematoma and perihaematomal oedema, which are associated with coagulation cascade activation, cell death and blood–brain barrier disruption [66]. Global cerebral oedema associated with a direct effect of bleeding and rebleeding is the major cause of death in SAH [67]. Given these complex mechanisms for injury after haemorrhagic stroke, corticosteroids might exhibit limited role in improving outcome. In contrast, cerebral oedema in patients with TBI is thought to be associated with impaired perivascular fluid drainage [68], which is distinct from brain swelling in stroke. Therefore, the pathophysiological differences between these conditions could explain the varying effects of corticosteroids on mortality.

Implications for clinical practice and future research directions

The findings of this study imply the potential of corticosteroids to reduce death in patients with ischaemic stroke, with alleviation of complications such as pneumonia. However, this finding was largely driven by a single large scale trial, which provides insufficient evidence to modify current guidelines. In addition, corticosteroids increased risk of hyperglycaemia, fever, and electrolyte disturbances, which are common adverse events and warrant careful monitoring in practice. Corticosteroids increased the risk of death after TBI and showed no effect for patients with haemorrhagic stroke, for which the current evidence did not support the routine use in these patients.

Future research is expected to identify individual patient who might benefit from corticosteroids, for example, patients who have received thrombectomy and achieved recanalization, or those who at high risk of

Table 2 Meta-analysis of the adverse drug events of corticosteroids for treatment of stroke and traumatic brain injury

Adverse events	Studies	Sample size	OR/MD (95% CI)	*P* values	*df*	I^2
Ischaemic stroke						
Gastrointestinal bleeding[a]	4	2343	0.83 (0.45, 1.56)	0.57	3	38%
Infections						
Any type of infections[a]	1	556	0.94 (0.68, 1.32)	0.73	0	0%
Pneumonia[a]	1	1680	0.70 (0.58, 0.85)	**0.0003**	0	0%
Hyperglycaemia/Diabetes mellitus[a]	2	2236	1.55 (1.02, 2.34)	**0.04**	1	0%
Cardiac problems[a]	1	556	1.39 (0.98, 1.97)	0.07	1	0%
Intracerebral haemorrhage						
Gastrointestinal bleeding[a]	4	384	1.67 (0.71, 3.91)	0.24	3	0%
Infections						
Any type of infections[a]	3	146	1.04 (0.24, 4.58)	0.96	2	55%
Pneumonia[a]	1	93	1.51 (0.44, 5.15)	0.51	0	0%
Sepsis[a]	1	93	7.64 (0.38, 152.24)	0.18	0	0%
Urinary tract infection[a]	1	93	2.09 (0.18, 23.89)	0.55	0	0%
Fever[a]	1	225	2.06 (1.12, 3.77)	**0.02**	0	0%
Perianal abscess[a]	1	93	3.13 (0.12, 78.88)	0.49	0	0%
Electrolytes disturbance						
Hyperkalaemia[a]	1	225	0.16 (0.05, 0.53)	**0.002**	0	0%
Hypokalaemia[a]	1	225	0.66 (0.26, 1.67)	0.38	0	0%
Hyponatremia[a]	1	225	2.02 (0.77, 5.25)	0.15	0	0%
Daily potassium excretion (mEq/day)[b]	1	28	54.10 (43.68, 64.52)	**< 0.00001**	0	0%
Serum potassium (mEq/L)[b]	1	28	-0.40 (-0.47, -0.33)	**< 0.00001**	0	0%
Total protein (mg/dL)[b]	1	28	-0.40 (-0.47, -0.33)	**< 0.00001**	0	0%
Hyperglycaemia/Diabetes mellitus[a]	3	344	1.56 (0.52, 4.65)	0.43	2	21%
Rising of blood pressure[a]	1	225	1.33 (0.63, 2.79)	0.46	0	0%
Subarachnoid haemorrhage						
Gastrointestinal bleeding[a]	5	329	1.37 (0.47, 3.97)	0.57	0	0%
Infections						
Any type of infections[a]	2	585	1.11 (0.18, 6.91)	0.91	1	92%
Pneumonia[a]	2	515	1.59 (0.44, 5.77)	0.48	1	79%
Sepsis[a]	2	585	1.50 (0.50, 4.50)	0.47	1	22%
Urinary tract infection[a]	2	515	1.18 (0.21, 6.68)	0.85	1	86%
Meningitis/Ventriculitis[a]	3	791	1.08 (0.26, 4.52)	0.92	2	57%
Surgical site infection[a]	1	309	1.03 (0.09, 11.49)	0.98	0	0%
Electrolytes disturbance[a]						
Decreased plasma volume (> 10%) at day 6[a]	1	62	0.69 (0.23, 2.06)	0.51	0	0%
Decreased plasma volume (> 10%) at day 12[a]	1	46	0.35 (0.08, 1.56)	0.17	0	0%
Negative cumulative fluid balance in first 6 days of treatment[a]	1	78	1.87 (0.41, 8.43)	0.42	0	0%
Negative cumulative fluid balance in entire 12-day period of treatment[a]	1	62	0.26 (0.03, 2.46)	0.24	0	0%
Negative cumulative sodium balance at first 6 days of treatment[a]	1	77	0.37 (0.15, 0.92)	**0.03**	0	0%
Negative cumulative sodium balance in entire 12-day period of treatment[a]	1	61	0.17 (0.06, 0.53)	**0.002**	0	0%
Hypokalaemia[a]	2	58	4.62 (1.45, 14.70)	**0.01**	1	0%
Hyponatremia[a]	2	58	0.09 (0.02, 0.58)	**0.01**	1	0%
Increased urine volume (more than 10 L/d)[a]	1	28	0.05 (0.00, 0.90)	**0.04**	0	0%
Hyperglycaemia/Diabetes mellitus[a]	7	799	2.01 (1.39, 2.92)	**0.0002**	3	0%
Blood glucose (mmol/L)[b]	1	28	1.88 (1.56, 2.20)	**< 0.00001**	0	0%
Traumatic brain injury						
Gastrointestinal bleeding[a]	9	1582	0.95 (0.44, 2.07)	0.91	8	0%

Table 2 (continued)

Adverse events	Studies	Sample size	OR/MD (95% CI)	*P* values	*df*	I^2
Infections[a]						
Any type of infections	4	907	0.96 (0.65, 1.41)	0.83	3	37%
Pneumonia	4	622	0.94 (0.36, 2.44)	0.9	3	75%
Sepsis	1	328	0.89 (0.37, 2.16)	0.8	0	0%
Urinary tract infection	1	328	0.83 (0.43, 1.61)	0.59	0	0%
Meningitis/Ventriculitis	1	328	1.49 (0.25, 9.04)	0.66	0	0%
Surgical site infection[a]	1	328	0.74 (0.16, 3.34)	0.69	0	0%
Hyperglycaemia/diabetes mellitus[a]	2	472	0.93 (0.63, 1.38)	0.71	1	0%
Blood glucose (mmol/L)[b]	1	104	1.49 (1.38, 1.60)	**< 0.00001**	0	0%

[a] Odd ratio (OR) for dichotomous outcomes

[b] Mean difference (MD) for continuous outcomes

brain swelling. In concern of safety, future studies should investigate optimal dose and treatment duration to balance potential therapeutic benefits against the risk of complications. Furthermore, further trials are needed to explore complementary therapies that might minimise the adverse effects of corticosteroids.

Limitations

We had assumed heterogeneity of included studies and used the random-effects modelling for pooled estimates. We also conducted subgroup analyses to explore potential sources of heterogeneity. However, there was heterogeneity remained within some subgroups, which might be attributed to differences in participant populations, study designs, and publication bias. This may influence the reliability of the results.

Our review had limitations. First, although the current study systematically searched and included relevant studies, we did not include grey literature, which may introduce publication bias. In addition, 60% of the included studies were published before 1980s. CT was introduced for the diagnosis of neurological diseases in 1972 [69]. Of the included studies, the first study diagnosed ischaemic stroke by CT was in 1976 [24], and for ICH [31] and SAH [42] were both in 1987. This may lead to inaccuracy in differential diagnosis of ischaemic stroke and haemorrhagic stroke [70]. Second, we had intended to include studies reporting any efficacy or safety outcomes; however, due to the diversity in outcome measures reported, we focused studies that had reported death, functional outcomes, or adverse events, since these are critical clinical outcomes after stroke and TBI. Third, although we found the benefit of corticosteroids on death after ischaemic stroke, this finding was largely driven by the results from a single large-scale trial of patients who had received thrombectomy and tested corticosteroids as an adjunctive therapy. More trials are needed to confirm the benefit of corticosteroids in patients with ischaemic stroke, and clarify their clinical characteristics.

Conclusions

Corticosteroids reduced the risk of death after in some patients with stroke, such as those with large artery occlusion after thrombectomy, but increased the risk of death after TBI, had no effect on functional outcomes after stroke and TBI. Further trials are needed to identify individual stroke patients who may benefit from corticosteroids, by clarifying the patient characteristics and refining treatment regimen.

Supplementary Information

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Additional file 1: Supplementary material.

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None.

Authors' contributions

SW: contribution to concept and design, acquisition, analysis, or interpretation of data, drafting and revising the manuscript, critical review of the manuscript for important intellectual content, and has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. YW: contribution to acquisition, analysis, or interpretation of data, drafting and revising the manuscript, critical review of the manuscript for important intellectual content. LH: contribution to acquisition, analysis, or interpretation of data, and critical review of the manuscript for important intellectual content. JL: contribution to acquisition, analysis, or interpretation of data, and critical review of the manuscript for important intellectual content. JD: contribution to critical review of the manuscript for important intellectual content. XP: contribution to critical review of the manuscript for important intellectual content. BM: contribution to concept and design, and critical review of the manuscript for important intellectual content. CA: contribution to concept and design, and critical review of the manuscript for important intellectual content. ML: contribution to critical review of the manuscript for important intellectual content.

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Data availability

The data used in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

As no individual patient-level data were used, institutional review board approval and informed consent were not required.

Consent for publication

Not applicable.

Competing of interests

The authors declare that they have no competing interests.

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